# State of the Globe: The Immunological Quest for an HIV/AIDS Vaccine Continues

Ever since the first acquired immune deficiency syndrome (AIDS) case was detected over three decades ago, AIDS has remained one of the most important causes of premature death, disability, as well as huge healthcare costs incurred, particularly for the world's poorest countries. AIDS is caused by the human immunodeficiency virus (HIV), and currently, over 33 million people worldwide are estimated to be living with HIV/AIDS, of which approximately 95% live in developing countries. Since a large proportion of the HIV-infected population is in their prime of life, the disease has a direct impact on the economic development of a country. Moreover, since the disease disproportionately affects the poor and deprived, it involves a vicious cycle that leads to further misery for the afflicted.

The introduction of highly active anti-retroviral therapy (HAART) has altered the scenario of AIDS, from being an inevitably fatal disease to a chronic and lingering infectious disease. With the advent of the HAART era, there has been an emphasis on living a healthier, longer, and more meaningful life. However, the cost of treatment remains high and will increase further with the change in policy of instituting HAART at higher CD4+ counts (350–500 cells/mm$^2$ or even higher) than previously recommended, thereby making more patients eligible for receiving the treatment. With the passage of time, more and more patients on first-line anti-retrovirals will require second-line drugs, thereby adding to the financial burden of the already overburdened health system of developing countries. In spite of the fact that prevention programs are already underway, ~1.8 million people died from complications of AIDS in 2009, with more than 2.6 million people becoming newly infected with HIV in the same year.

There are many factors that facilitate and accelerate the spread of HIV infections. The obvious transmission is through the sexual route. In this regard, many susceptible populations have been identified through years of painstaking research. These include female sex workers (FSWs), men who have sex with men (MSM) and intravenous drug users (IVDUs). Other complicating factors include the issue of co-infection with other infectious diseases such as tuberculosis, which greatly complicates the management of the diseases.

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In the absence of an effective biomedical option for preventing HIV infections, the various National AIDS Control Programs have relied heavily on the promotion of condoms and behavioral change for reducing high-risk behavior through information, education and communication (IEC) activities. However, the various interventions and strategies aimed at bringing about behavioral changes have had a limited impact in different settings. Moreover, sustainability as well as replicability of such interventions has always been difficult. Hence, researchers should not lose focus on developing biomedical interventions for preventing HIV transmission. The search for such interventions has in recent years yielded encouraging results. A number of trials have evaluated the efficacy of various preventive strategies that have exhibited protection against sexual transmission of HIV. Two of these include male circumcision in South Africa (57% efficacy) and treatment against sexually transmitted infections (STI) in Tanzania (42% efficacy). Microbicides constitute an important women-controlled method for the prevention of sexual transmission of HIV, as well as other STIs. A microbicide trial based on a 1% vaginal gel formulation of tenofovir conducted by the Centre for the AIDS Programme of Research in South Africa (CAPRISA 004 Tenofovir Gel Trial) has proven to be effective in reducing HIV acquisition by an estimated 39% overall, and by 54% in women with high adherence to the microbicide intervention. Further trials to confirm the efficacy of the gel are planned. However, microbicides trials have not always been successful. The PRO 2000 Trial is a case in point. PRO 2000 is a 0.5% microbicidal gel for intravaginal use, prior to sexual intercourse. Although initial trials of PRO 2000 in African women suggested that it had the potential to prevent HIV transmission, a subsequent large-scale study – the MDP 301 Trial – the largest microbicide trial so far, with more than 9000 participants, found no evidence that PRO 2000 reduced women's risk of infection to HIV.

Vaccines are regarded as the most cost-effective public health interventions to have been invented. Vaccination has been successfully applied for the eradication of

smallpox, as well as the near-eradication of polio, and also for controlling many other infectious diseases. A cheap and efficacious vaccine will go a long way in controlling the AIDS pandemic, particularly for resource-limited settings. However, in spite of sustained global efforts, a cost-effective AIDS vaccine is currently not available. There are many factors that act as hurdles or hindrances toward achieving the goal of developing a cost-effective AIDS vaccine. Among the great many hurdles is the lack of scientific knowledge about the nature and level of the immune responses that would be required to achieve protection against HIV infection as well as to halt its progression to full-blown AIDS. Hence, AIDS vaccine strategies adopted till date have aimed at eliciting a balanced immune response involving both arms of the adaptive immune system, namely, humoral as well as cellular. Long-lasting, high-titer, broadly neutralizing antibodies are desirable for the prevention of HIV acquisition, whereas cytotoxic T lymphocyte (CTL) responses are required for the better control of the vial load following infection, thereby slowing down the progression toward full-blown AIDS. Moreover, CTL responses are likely to decrease the chance of secondary transmission. Other factors that have hindered the progress in the development of an effective AIDS vaccine include the absence of relevant and predictive animal models and the complexities related to the preparation and conduct of multiple large-scale clinical trials with particular reference to developing countries.

In spite of the hurdles, various AIDS vaccine candidates for inducing either CTL or neutralizing antibodies or both are being developed and tested. These include various experimental DNA vaccines, viral vectored vaccines and peptide-subunit vaccines, which are being tested alone or in a combined prime-boost approach. The first Phase I clinical trial of an AIDS vaccine was conducted in USA in 1987. Since then, more than 35 candidate AIDS vaccines have been tested in over 65 Phase I/II clinical trials, involving more than 10,000 healthy human volunteers, in more than 19 countries. Additionally, three large-scale Phase III clinical trials have been carried forward to completion. However, only the ALVAC®/AIDSVAX® prime-boost combination vaccine demonstrated a marginal protective effect in the RV144 Phase III clinical trial conducted in Thailand, in which ALVAC® was used for priming and AIDSVAX® for boosting. In spite of these large numbers of studies, an ideal AIDS vaccine still eludes us. Moreover, the failure of the VaxGen and STEP Trials has made the scientific community think twice and take a fresh look at the biology of HIV, vaccine design strategies, and also clinical trial methodologies.

Because of the highly variable nature of the virus, sequences of different subtypes cluster apart and vaccines based on one subtype may not show efficacy against other subtypes. Hence, it is envisaged that vaccine candidates based on multiclade constructs or on subtypes prevalent in particular countries/areas would be more appropriate. The study published by Shete and colleagues in this issue is therefore of particular importance in the Indian context, considering the high disease burden, as well as the paucity of studies based on the Indian subtype C. During the chronic phase of infection, HIV undergoes a series of mutations that help it to escape from the host immune response, as opposed to HIV found in acutely infected patients, which represents transmitted viruses. Such transmitted viruses constitute an important basis for vaccine design as they represent viruses that have not undergone genetic changes in the absence of immune pressure. The group has used sequences from recently transmitted HIV strains to develop a vaccine candidate. The *gag* is a relatively conserved gene and host responses to *gag* have been found to be associated with the protection against progression to full-blown AIDS. Hence, HIV *gag* has been used as a major target in many of the vaccine studies. It has been observed that not all portions of *gag* can induce immune responses and certain regions are found to be highly immunogenic, inducing immune responses in a majority of HIV-infected patients. Such immunodominant regions harbor frequently identified epitopes and might constitute an important component for vaccine design. The study reports that the epitopes identified by BALB/c mice lie within the immunodominant region of *gag* and therefore highlights the importance of targeting this region.

India has so far conducted three Phase I AIDS vaccine trials under the collaborative initiative of the Indian Council of Medical Research (ICMR), the National AIDS Control Organization (NACO), and the International AIDS Vaccine Initiative (IAVI). This initiative has resulted in developing the local capacity to undertake AIDS vaccine trials in India. However, these trials were conducted using AIDS vaccine candidates that were developed outside India, the majority using non-Indian gene sequences. There are several laboratories in India currently working toward the development of indigenous AIDS vaccine candidates that may be more appropriate for the Indian context. The data generated from these laboratories will be very crucial for the Indian AIDS Control Program in the future.

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